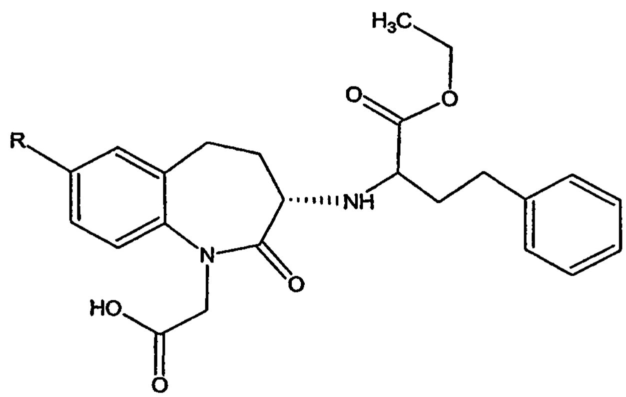
PROCESS FOR PREPARATION OF BENAZEPRIL

Field of the Invention

The present invention relates to a process for preparation of benazepril of Formula I, wherein R is hydrogen or pharmacologically acceptable salt thereof by eliminating the impurity of 7-bromo analogue of benazepril of Formula Ia, wherein R is bromo group.

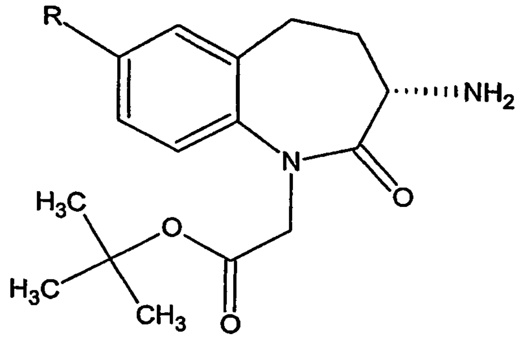


FORMULA I (R = H)
FORMULA Ia (R = Br)

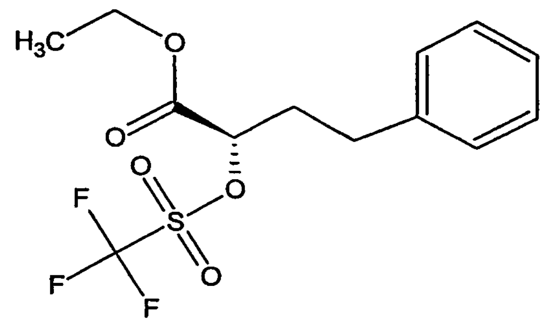
Background of the Invention

Benazepril is chemically (3S)-1-(carboxymethyl)-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl] amino]-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one of Formula I as shown in the accompanied drawing. It is a well-known long acting angiotensin-converting enzyme (ACE) inhibitor primarily used for the treatment of hypertension. Benazepril was presumably reported for the first time in US Patent No. 4,410,520.

Two key intermediates in the preparation of benazepril are, 3-(S)-amino-1-carboxymethyl-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one or its 1-carboxymethyl protected derivatives of Formula II and ethyl (R)-2-hydroxy-4-phenylbutyrate or its activated analogues of Formula III. These two intermediates are condensed in presence of a base to get benazepril.



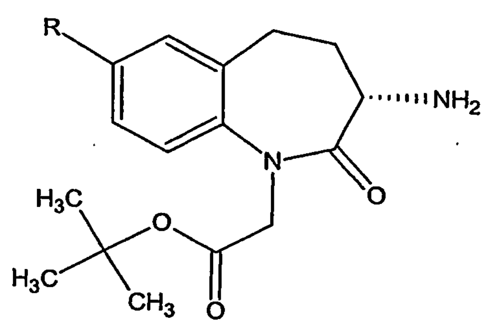
FORMULA II (R = H)



FORMULA III

Indian patent application 374/DEL/2001 describes a process for the preparation of benazepril. The trifluoromethane sulphonic ester of ethyl (R)-2-hydroxy-4-phenylbutyrate of Formula III is condensed with 1-t-butyloxycarbonylmethyl-3-(S)-amino-2,3,4,5-tertrahydro-1H-[1]benzazepin-2-one (herein onwards referred as II) in the presence of a halogenated organic solvent, such as methylene chloride and N-methyl morpholine followed by treatment of the resultant crude oil obtained with dry hydrogen chloride gas to give benazepril hydrochloride.

Even though the process described in the above patent application starts with an intermediate compound of Formula II, the purity of this intermediate can be of great concern. An impurity of 7-bromo-1-t-butyloxycarbonylmethyl-3-(S)-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (hereinafter referred as impurity of Formula IIa) is typically present in the reaction product between 3 to 8%.



FORMULA IIa (R = Br)

The purification of the compound of Formula II is therefore required which results in lower overall yield. If the compound of Formula II is used as such, without purification to remove the impurity of Formula IIa, in the preparation of benazepril a corresponding impurity of Ia can result, at levels of between 2 to 5%. Removal of this impurity from

final product is very difficult requiring several purification stages, which again results in lower overall yield.

US Patent No. 4,575,503 discloses a synthesis of benazepril. The process described produces benazepril in fairly low yield. Further the presence of IIa and Ia in final benazepril and its removal is not discussed in this patent.

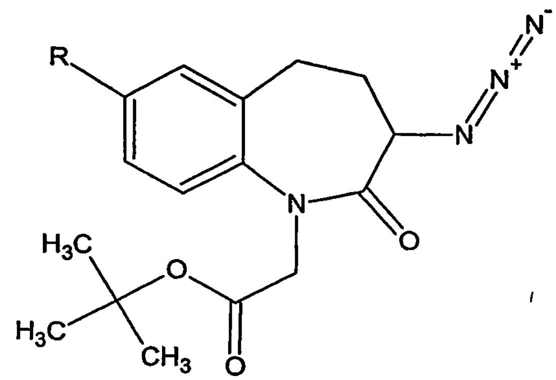
US Patent No. 4,692,522 provides benzofused lactams which are CCK antagonists, wherein preparation of intermediate II is disclosed. The process however, does not disclose the synthesis of benazepril or pharmaceutically acceptable salts thereof using II. Also the quantities of raw materials described for preparation of II are significantly high which is not economical from the commercial point of view.

Summary of the Invention

The present inventors now find that it is possible to prepare a highly pure benazepril of Formula I or its physiologically acceptable salts, which is devoid or essentially devoid of its 7-bromo analogue of Formula Ia. The objective can be achieved by using pure 3-(S)-amino-1-carboxymethyl-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one or its 1-carboxymethyl protected derivatives of Formula II, which in turn is devoid or essentially devoid of corresponding 7-bromo analogue of Formula IIa.

While working on the problem, the present inventors have removed the impurity of Formula IIa from compound of Formula II by reductive dehalo-hydrogenation using noble metal catalyst in presence of hydrogen or source of hydrogen. The so-obtained compound of Formula II, which does not contain any detectable quantity of the impurity of Formula IIa, is treated with compound of Formula III in presence of a base to get highly pure compound of Formula I or its physiologically accepted salts.

In turn, the desired compound of Formula II having no detectable impurity of Formula IIa is prepared by hydrogenating 3-azido t-butyl ester of Formula IV containing the 7-bromo-3-azido impurity of Formula IVa, up to about 8% in the presence of Raney nickel in methanol to get racemic compound of Formula II containing the impurity of Formula IIa, which after dehalo-hydrogenation over palladium on carbon in methanol gave pure racemic compound of Formula II, wherein the corresponding IIa impurity is not only removed but also essentially completely converted to the desired compound of Formula II.



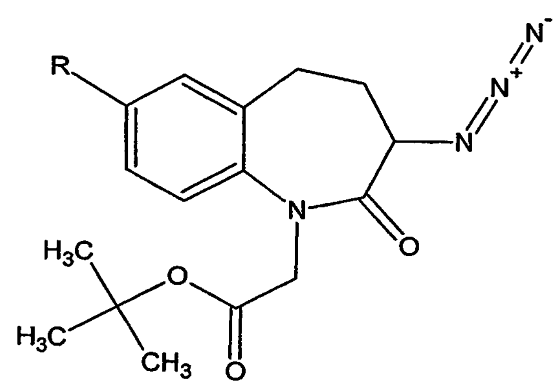
FORMULA IV (R = H)
FORMULA IVa (R = Br)

The yield of benazepril as prepared according to the process provided herein is increased, as the yield of intermediate (S)-II is further increased during the hydrogenation with palladium on carbon where even the undesired 7-bromo-3-azido impurity of Formula IVa is not only removed but also converted to the required intermediate.

Detailed Description of the Invention

One aspect provides a process for preparation of highly pure compound of Formula II having no detectable quantity of impurity of Formula IIa, wherein the process includes,

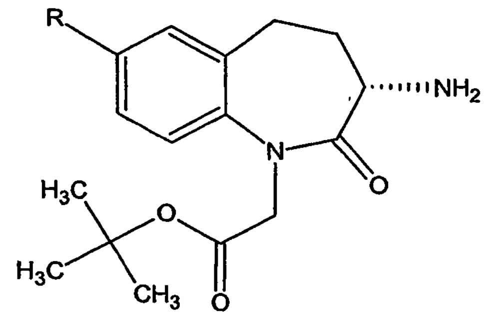
a) hydrogenating a compound of Formula IV containing up to about 8% of impurity of Formula IVa in presence of noble metal catalyst



FORMULA IV (R = H)
FORMULA IVa (R = Br)

b) isolating highly pure racemic compound of Formula II having no detectable quantity of impurity of Formula IIa, and

c) optionally resolving the racemic compound of Formula II with its component stereoisomers.



FORMULA II (R = H)
FORMULA IIa (R = Br)

The starting material 3-azido t-butyl ester of Formula IV can be prepared using methods described by Blicke et al., *J. Am. Chem. Soc.*, 76, 2317 (1954); Brenner et al., *Helv. Chem. Acta*, 41, 181 (1958) and Green et al., "Protecting Groups in Organic Synthesis," John Willey and Sons, New York (1998). The 7-bromo-3-azido impurity of Formula IVa is typically present in this material in amounts of, for example, up to about 8%, for example, from about 2% to about 8%, or from about 3% to about 8%. The purification of this intermediate is not carried out. The processes described herein are suitable for preparing highly pure compounds when the amount of impurities (by wt. %) found in starting materials or intermediates are greater than specified herein.

The hydrogenation at step (a) is performed using a metal catalyst, which may be selected from palladium on carbon, platinum oxide, platinum black, palladium acetate, rhodium on carbon and the like. The palladium on carbon catalyst is commercially available in several strengths ranging from 1 to 10% of palladium adsorbed on carbon. The source of hydrogen can be hydrogen gas or compounds which generate hydrogen gas when used in hydrogenation. The source of hydrogen can be selected from a group comprising ammonium formate, formic acid, alkali metal formats such as sodium formate, potassium formate. When such compounds are used as source of hydrogen, the reaction can be carried out at atmospheric pressure and at a lower temperature.

Step (a) can be conveniently carried out in an organic solvent selected from alkanols, esters and cyclic ethers or mixtures thereof. The alkanols include methanol,

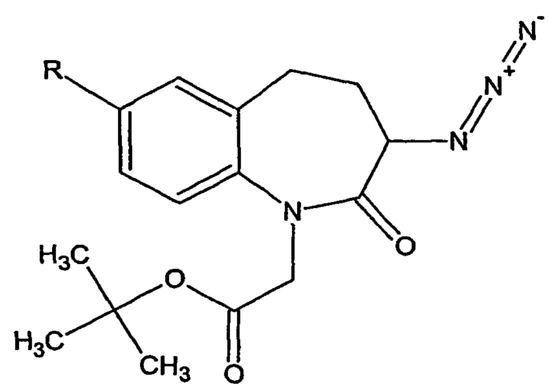
ethanol, propanol and isopropanol or mixtures thereof. The temperature range of hydrogenation reaction can be between 10 to 60°C.

The product (II) is then isolated from the reaction mass by filtration of catalyst followed by concentration of the solvent. Optionally the residue obtained can be treated with second organic solvent in which (II) is insoluble or slightly soluble. The separated (II) is then filtered and dried.

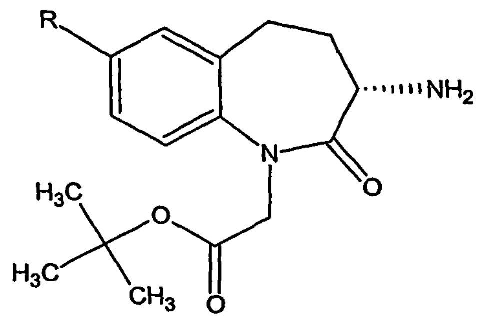
In this process, two changes are achieved in a single reaction. Firstly, the 3-azido groups present in the starting material as well as in the impurity are reduced to 3-amino group, and secondly the 7-bromo group present in the impurity is cleaved. In fact, the impurity of Formula IVa, after subjecting it to hydrogenation using noble metal catalyst, gives the desired racemic compound of Formula II.

A second aspect provides a process for preparation of highly pure compound of Formula II having no detectable quantity of impurity of Formula IIa, wherein the process includes,

a) hydrogenating a compound of Formula IV containing up to about 8% of impurity of Formula IVa in presence of Raney nickel to yield the racemic compound of Formula II containing up to about 8% of impurity of Formula IIa;



FORMULA IV (R = H)
FORMULA IVa (R = Br)



FORMULA II (R = H)
FORMULA IIa (R = Br)

b) hydrogenating the product of step a) in presence of a noble metal catalyst;

c) isolating the racemic compound of Formula II having no detectable quantity of the impurity of Formula IIa; and

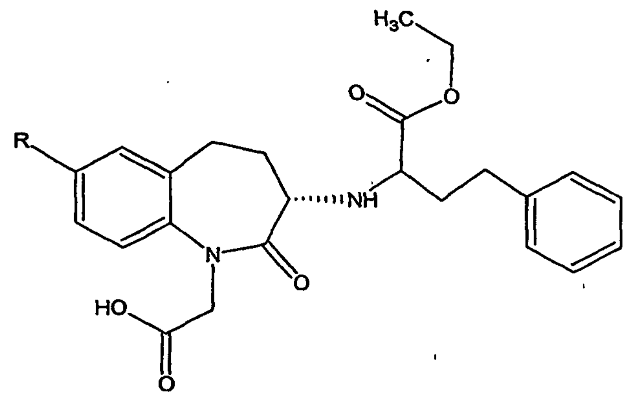
d) optionally resolving the racemic compound of Formula II into its component stereoisomers.

The azido group present in the compound of Formula IV as well as the impurity of Formula IVa is reduced using Raney nickel in presence of hydrogen or a source of hydrogen. After completion of that reaction, the catalyst is removed, for example, by filtration, and the organic solvent is concentrated to get the racemic compound of Formula II containing the impurity of Formula IIa.

The reaction can be conveniently carried out in alcoholic solvents, which include, for example, methanol, ethanol and isopropanol or mixtures thereof. The reduction can also be carried out in formic acid, acetic acid and the like. The source of hydrogen can be selected from, for example, ammonium formate, formic acid, alkali metal formate such as sodium formate, potassium formate. When such compounds are used as source of hydrogen, the reaction can be carried out at atmospheric pressure and at a lower temperature.

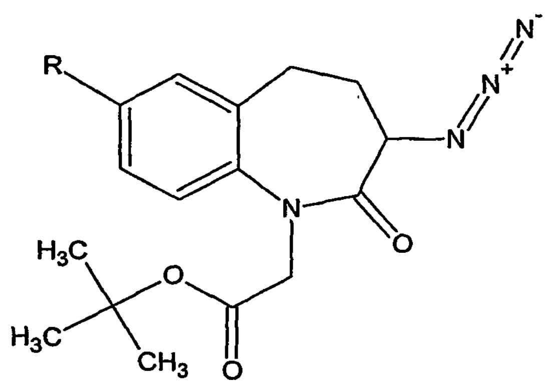
Raney nickel as catalyst is not capable of removing the aromatic halogen and therefore step b) can be performed wherein the compound of Formula II containing about 8% of the impurity of Formula IIa is hydrogenated further using noble metal catalyst. The reaction conditions and isolation process are similar to that discussed in first aspect.

A third aspect provides processes for the preparation of highly pure compound of Formula I or a pharmaceutically acceptable salt, solvate and hydrate thereof, having no detectable quantity of impurity of Formula Ia, wherein the process includes

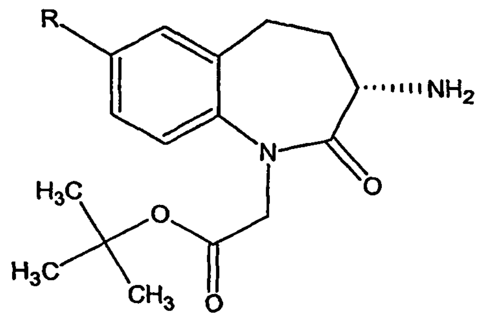


FORMULA I (R = H)
FORMULA Ia (R = Br)

a) hydrogenating a compound of Formula IV, optionally containing up to about 8% of impurity of Formula IVa, in the presence of a metal catalyst and isolating the racemic compound of Formula II which is optionally devoid of the corresponding IIa impurity.



FORMULA IV (R = H)
FORMULA IVa (R = Br)

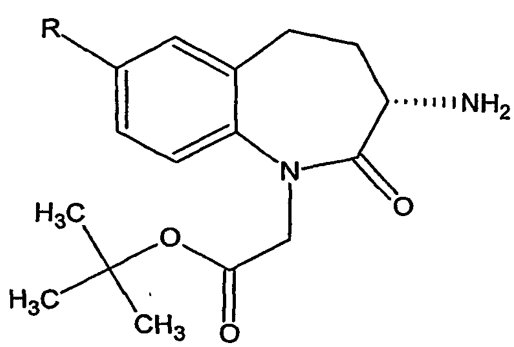


FORMULA II (R = H)
FORMULA IIa (R = Br)

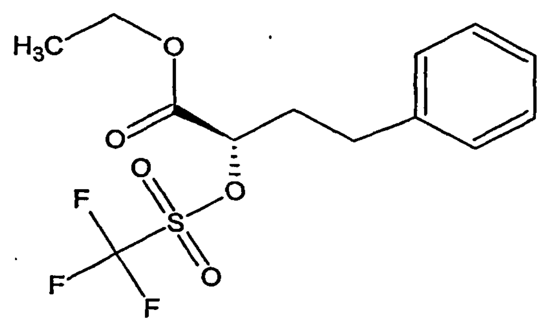
b) hydrogenating the racemic compound of Formula II, optionally containing up to about 8% of IIa, in presence of a noble metal catalyst to get highly pure racemic compound of Formula II having no detectable amount of impurity of Formula Ia.

c) converting the highly pure racemic compound of Formula II to the highly pure (S) enantiomer of the compound of Formula II by chiral resolution using tartaric acid.

d) condensing the (S) enantiomer of the compound of Formula II with III in presence of an organic solvent and a base to get highly pure compound of Formula I or physiologically acceptable salt, solvates or hydrates thereof.



FORMULA II (R = H)

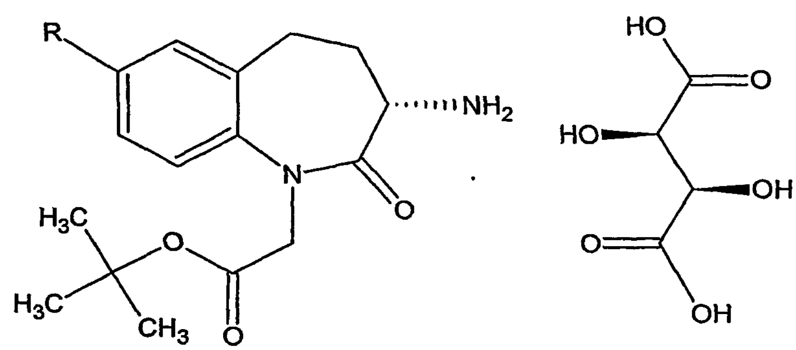


FORMULA III

The hydrogenation at step (a) is performed using a metal catalyst, which may be selected from palladium on carbon, platinum oxide, platinum black, palladium acetate, rhodium on carbon, Raney nickel and the like. The hydrogenation in step b) can be optional. For example, it must be performed when the hydrogenation in step a) is performed with Raney nickel. When step a) is performed using palladium on carbon as

metal catalyst, for example, step b) can be omitted. The metal catalysts used in this step can be, for example, palladium on carbon, platinum oxide, platinum black, palladium acetate, or rhodium on carbon. Other conditions, such as source of hydrogen, solvent and reaction temperature, are similar to that mentioned above in the first and second aspects.

Racemic mixtures of prochiral amines can be converted to their diastereomeric salts by treating them with chirally active organic acids. The mixture of diastereomers can then be separated by suitable means, such as crystallization or chromatography. The desired diastereomer salt can then be converted back to a chiral amine by treating it with a base. The chiral resolution at step c) is performed to get the desired (S) enantiomer of a compound of Formula II. Organic acid used can be, for example, chirally active L-(+)-tartaric acid. The organic solvent used in the salt formation can be selected from alkanol, ester, ether and ketone or a mixture thereof. The alkanol can be selected from, for example, methanol, ethanol, propanol and isopropanol or mixtures thereof. Seeding the reaction mixture with pure (S) enantiomer of a compound of Formula V followed by cooling can effect the crystallization of the pure (S) enantiomer of a compound of Formula V salt.



(S)-V SALT

The (S) enantiomer of a compound of Formula V salt is hydrolyzed to generate the free (S) enantiomer of a compound of Formula II. This is achieved by treating (S) enantiomer of a compound of Formula V salt with a base in presence of water or an organic solvent selected from polar protic or polar aprotic solvents. The pH of the reaction mass after addition of the base can be adjusted to a value between about 7.5 and about 12. The base used can be an inorganic base such as sodium or potassium hydroxide, sodium or potassium carbonate, sodium or potassium bicarbonate. Ammonia or ammonium hydroxide can also be used as bases. The organic bases such as triethylamine,

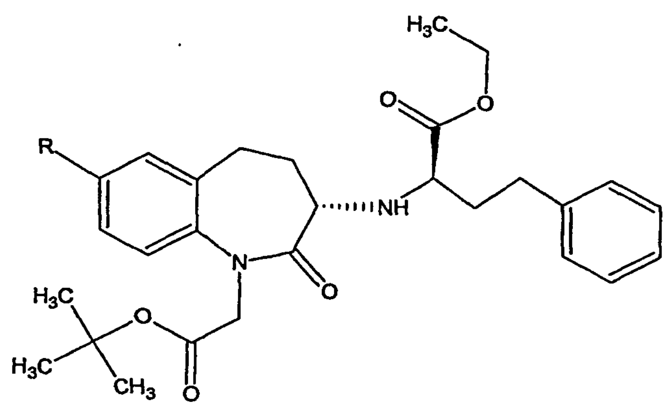
diisopropylamine, and cyclohexylamine can be used. The product is then extracted in a halogenated organic solvent such as methylene chloride or chloroform and the solvent was removed by vacuum distillation. The residue can then be isolated from the residue by addition of another solvent, selected from, for example, diethyl ether, diisopropyl ether, cyclohexane, hexane and heptane or mixtures thereof.

In step (d) highly pure compound of Formula II is treated with a compound of Formula III in presence of an organic solvent and a base. Intermediate compound of Formula III is prepared by method described in Indian patent application 374/DEL/2001.

The organic solvent for condensation in step d) can be selected from, for example, haloalkanes such as chloroform, carbon tetrachloride, methylene chloride, ethylene bromide and ethylene chloride or mixtures thereof.

The base used can be selected from, for example, pyridine and its derivatives, morpholine and its derivatives, trialkyl amines and cyclic amines or mixtures thereof.

Benazepril of Formula I or physiologically acceptable salts, hydrates and solvates thereof, can be prepared by treating a compound of Formula VI obtained after the reaction with an acid in an organic solvent. The protecting t-butyl group can be removed along with salt formation during this treatment.



FORMULA VI (R = H)

The acid can be hydrochloric acid used as a gas and purged through the solution of the compound of Formula I in an organic solvent, or can be a solution of hydrogen chloride gas in an organic solvent. The organic solvent can be alkanol such as methanol, ethanol, isopropanol or ester such as ethyl acetate, ethyl formate, isopropyl acetate or

ketone such as acetone, or ether such as diethyl ether, diisopropyl ether, tetrahydrofuran or mixtures thereof.

The crude I obtained can be subjected to solvent crystallization. The solvents for crystallization include alkanol such as methanol, ethanol, propanol and isopropanol or esters such as ethyl acetate, ethyl formate, butyl acetate or ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone, diisobutyl ketone or mixtures thereof.

A fourth aspect provides highly pure compound of Formula II having no detectable quantity of impurity of Formula IIa as determined by a sensitive HPLC method.

A fifth aspect provides highly pure benazepril of Formula I or physiologically acceptable salt, solvate and hydrate thereof having no detectable quantity of impurity of Formula Ia as determined by a sensitive HPLC method.

A sixth aspect provides a process of preparation of benazepril of Formula I or physiologically acceptable salt, solvate and hydrate thereof wherein highly pure compound of Formula II having no detectable quantity of impurity of Formula IIa is used as an intermediate.

A seventh aspect provides pharmaceutical compositions comprising highly pure benazepril of Formula I or physiologically acceptable salt, solvate and hydrate thereof having no detectable quantity of impurity of Formula Ia along with a pharmaceutically acceptable carriers or diluents.

An eighth aspect provides a method of antagonizing angiotensin-converting enzyme (ACE) wherein the said method comprises of administering to a mammal in need thereof a therapeutically effective amount of highly pure benazepril of Formula I or physiologically acceptable salt, solvate and hydrate thereof having no detectable quantity of impurity of Formula Ia.

In the following examples, the preferred embodiments of the present invention are described only by way of illustrating the process of the invention. However, these do not limit the scope of the present invention any way.

Chromatographic Parameters

The column used was Kromasil C-18, 5μm (150 mm x 4.6 mm). The mobile phase was a gradient, which started as 60% phosphate buffer (pH 5.6) : 20% methanol : 20% tetrahydrofuran. At 20 minutes, the gradient has continuously changed to 30%

buffer : 50% methanol : 20% tetrahydrofuran. At 25 minutes the gradient has continuously changed to 60% buffer : 20% methanol : 20% tetrahydrofuran, where the gradient remain until 35 minutes after the 20 μL injection. The flow rate is 1.0 mL/minute. Detection is at 240 mm.

By these parameters the Limit of Detection for the compound of Formula IIa was 3ppm, for the compound of Formula IVa was 5ppm, and for the compound of Formula Ia was 0.006% w/w.

Blank solution was prepared by diluting 5 mL of methanol with 50 ml of a 20 : 80 water : methanol solution (diluent). System suitability solution was prepared by weighing about 20 mg of 3(S)-amine-t-butyl ester working standard and transferring to a 50 mL VSL metric flask, dissolving in 5 mL of methanol, filling to the mark with diluent, and filtering. Sample solutions were similarly prepared. System suitability is met if and only if the USP Target for the 3(S)-amine-t-butyl ester pack is not less than 1500, and the USP Target for that pack is not more than 1.5.

<u>Example 1: Preparation of Highly Pure (±) 1-t-butyloxycarbonylmethyl-3-amino-2,3,4,5-tetrahydro-1h-[1]benzazepin-2-one of Formula II Using 10% Palladium on Carbon and Hydrogen Gas</u>

To a solution of 1-t-butyloxycarbonylmethyl-3-azido-2,3,4,5-tertrahydro-1H-[1]benzazepin-2-one of Formula IV (5 g, 15.8 mmol) containing 1-t-butyloxycarbonylmethyl-7-bromo-3-azido-2,3,4,5-tetrahydro-1H-[1]benzazepin -2-one of Formula IVa as impurity (7.67%) in methanol (25 ml) was added 10% palladium on carbon (0.5 g, 50% wet). The mixture was stirred at room temperature under hydrogen gas at a pressure of 40 to 50 psi with periodic venting. After 16 hours the reaction mass was filtered through celite bed to remove palladium on carbon and the filtrate was concentrated to dryness under vacuum to provide the title product as viscous oil which solidified on storage.

Yield: 4.5 g, 98%

Purity: 87.47%

Impurity IIa: Not detected by HPLC

Example 2: Preparation of Highly Pure (±) 1-t-butyloxycarbonylmethyl-3-amino-2,3,4,5-tetrahydro-1h-[1]benzazepin-2-one of Formula II using 10% Palladium on Carbon and Ammonium Formate as Source of Hydrogen

To a solution of 1-t-butyloxycarbonylmethyl-3-azido-2,3,4,5-tertrahydro-1H-[1]benzazepin-2-one of Formula IV (5 g, 15.8 mmol) containing 1-t-butyloxycarbonylmethyl-7-bromo-3-azido-2,3,4,5-tetrahydro-1H-[1]benzazepin -2-one of Formula IVa as impurity (7.67%) in methanol (25 ml) containing palladium on carbon catalyst (0.5 g, 10%, 50% wet) was added ammonium formate (10.0 g, 15.75 mmol). The temperature of the reaction mass was slowly raised to 40-50°C and stirred at this temperature for 16 hours. After confirming the reaction completion by TLC, the catalyst was removed by filtration and the filtrate was concentrated under vacuum and the residue was dissolved in methylene chloride (50 ml) and water (50 ml). The organic layer was separated and solvent removed under vacuum to get the title product as amorphous solid.

Yield: 4.55 g, 99%

Purity: 89.88%

Impurity IIa: Not detected by HPLC

Example 3: Preparation of Highly Pure (±) 1-t-butyloxycarbonylmethyl-3-amino-2,3,4,5-tetrahydro-1h-[1]benzazepin-2-one of Formula II

Part a: preparation of (±) 1-t-butyloxycarbonylmethyl-3-amino-2,3,4,5-tetrahydro-1h-[1]benzazepin-2-one of formula ii

To a solution of 1-t-butyloxycarbonylmethyl-3-azido-2,3,4,5-tertrahydro-1H-[1]benzazepin-2-one of Formula IV (5 g, 15.8 mmol) containing 1-t-butyloxycarbonylmethyl-7-bromo-3-azido-2,3,4,5-tetrahydro-1H-[1]benzazepin -2-one of Formula IVa as impurity (7.67%) in methanol (25 ml) was added Raney nickel (0.82 g). The mixture was stirred at 50-55°C under hydrogen gas at a pressure of 40 to 50 psi with periodic venting. After 16 hours the reaction mass was filtered through celite bed to remove Raney nickel and the filtrate was concentrated to dryness under vacuum to provide the title product as viscous oil which solidified on keeping.

Yield: 4.5 g, 98%

Purity: 87.47%

Impurity IIa: 5.28%.

Part B: Conversion of (±) 1-T-Butyloxycarbonylmethyl-3-Amino-2,3,4,5-Tetrahydro-1h-[1]Benzazepin-2-One of Formula Ii To Highly Pure (±) 1-T-Butyloxycarbonylmethyl-3-Amino-2,3,4,5-Tetrahydro-1h-[1]Benzazepin-2-One of Formula Ii

To a solution of 1-t-butyloxycarbonylmethyl-3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one of Formula II as obtained in Example 3, Part A (5 g, 17.24 mmol) containing 1-t-butyloxycarbonylmethyl-7-bromo-3-amino-2,3,4,5-tetrahydro-1h-[1]benzazepin-2-one of Formula IIa as impurity (5.28%) in methanol (25 ml) was added 10% palladium on carbon (0.5 g, 50% wet) and ammonium formate (10 g, 15.75 mmol). The mixture was stirred at room temperature. After 12 hours the reaction mass was filtered through celite bed to remove palladium on carbon and the filtrate was concentrated to dryness under vacuum to provide the title product as viscous oil. The oil obtained was further treated with dichloromethane (50 ml) and water (50 ml). The organic layer was cautiously treated with diluted sodium bicarbonate solution and solvent removed in vacuuo to give a residue which was further crystallized in ether to get the desired title compound

Yield: 4.75 g, 98%

Purity: 95%

Impurity IIa: Not detected by HPLC

<u>Example 4: Chiral Resolution Of Highly Pure (±)1-T-Butyloxycarbonylmethyl-3-Amino-2,3,4,5-Tetrahydro-1h-[1]Benzazepin-2-One Using Tartaric Acid</u>

Part A: Preparation of Highly Pure (S)-1-T-Butyloxycarbonylmethyl-3-Amino-2,3,4,5-Tetrahydro-1h-[1]Benzazepin-2-One Tartrate Salt of Formula V

Highly pure 1-t-butyloxycarbonylmethyl-3-amino-2,3,4,5-tetrahydro-1h-[1]benzazepin-2-one of Formula II (5.0 g, 17.24 mmol) was heated in ethanol (12.5 ml) at 50-55°C for 25 minutes. The temperature was further raised to 60-65°C and to this was added a solution of L-(+)-tartaric acid (1.8 g, 11.9 mmol) in ethanol (7.5 ml). The reaction mixture was stirred for 24 hours at 60-65°C, allowed to cool to 35-37°C and filtered at the same temperature to afford the crude product (2.75 g, 72%). This was suspended in alcohol (11 ml) and stirred at 62-65°C for 3 hours, allowed to cool to 45-47°C and filtered to afford the title compound.

Yield: 2.55 g, 93%

Purity: 99.87%

Part B: Generation of Highly Pure (S)-1-T-Butyloxycarbonylmethyl-3-Amino-2,3,4,5-Tetrahydro-1h-[1]Benzazepin-2-One of Formula Ii From Highly Pure Tartrate Salt

To a suspension of highly pure tartrate salt of Formula V (5.0 g, 11.36 mmol) in water (50 ml) gradually added ammonium hydroxide (~ 5 ml) drop-wise till the pH is about 9.0 to 9.2. The solution was stirred and to it added methylene chloride (12.5 ml). The reaction mixture was stirred for further 30 minutes and the layers were separated. The solvent was concentrated under vacuum to get residue, which was crystallized from ether to get title compound.

Yield: 2.6 g, 80%

Purity: 99.88%

Impurity IIa: Not detected by HPLC

Example 5: Preparation Of Highly Pure Benazepril Hydrochloride

Part B: Preparation of Highly Pure Benazepril T-Butyl Ester of Formula Vi

To a solution of trifluoromethane sulphonic ester of ethyl (R)-2-hydroxy-4-phenylbutyrate of Formula III in 15 ml of methylene chloride was added a solution of 5.67 gm of highly pure (S)-1-t-butyloxycarbonylmethyl-3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one of Formula II and 2.46 gm of N-methyl morpholine in methylene chloride drop-wise at room temperature. The reaction mixture was stirred for 2 hours. The completion of the reaction was monitored by HPLC. The reaction was quenched by addition of 40 ml of water and 60 ml of methylene chloride. The pH adjusted to 8.5 with 10% sodium bicarbonate solution. The organic layer was separated and washed twice with water. It was then dried over anhydrous sodium sulphate and solvent was distilled off to afford the title compound as an oily residue.

Part B: Preparation of Highly Pure Benazepril Hydrochloride

Through a solution of t-butyl ester of Formula VI in ethyl acetate cooled to about 10 to 12°C was purged dry hydrogen chloride gas slowly without allowing the temperature to rise. The salt formation was monitored by TLC and after completion of the reaction, excess hydrogen chloride and solvent was completely removed under vacuum. To the residue was added, 45 ml acetone and the resultant mixture was stirred for 1 hour at 5-8°C.

The product was filtered and dried to constant weight under vacuum at 45-50°C affording 8.27 gm of almost white product with a diastereoisomer ratio of SS:SR = 99.36:0.18. Yield 91.6%.

The product obtained was dissolved in methanol and treated with activated charcoal. The solution was filtered through celite bed to remove charcoal and then concentrated under vacuum to recover methanol to get a oily residue. Ethyl acetate was added to this residue drop-wise till slight haziness starts. The hazy solution was seeded with pure benazepril hydrochloride and stirred. More ethyl acetate was added drop-wise and cooled to about 5-10°C. The mixture was stirred for further 5 hours and the separated product was filtered. The slurry of wet product was stirred in ethyl acetate. The product was filtered and dried in a vacuum oven at 45-50°C to get highly pure benazepril hydrochloride.

Yield: 8.27 g, 91.9%

Diastereoisomer ratio of SS : SR = 99.36 : 0.18.

Purity: 99.75%

Impurity Ia: Not detected by HPLC.